Review of Data Related to the Evaluation of the Dow Capillary Membrane Oxygenator by the T & E Facilities

Based on:

1) IITRI report N7002-TSR-1 7 June 1971: Dow Capillary Oxygenator.
2) UBTL report TR 104-4-TO-001 9 October 1971: The DCMO -- An Assessment of Readiness for Clinical Testing as of 30 September 1971.
3) Dow Chemical Co. report NHLI-71-2360-1 10 August 1972: Annual report.
4) IITRI Topical report No. 1 17 November 1971: The Nature of Thrombus in a Hollow Fiber Oxygenator.
5) IITRI report NIH-NHLI-69-2125-1 1 February 1972: Annual Report.
6) Brown University report 9 June 1972: Summary report on Oxygenator Testing Dow series EDO.
7) UBTL report TR-104-5-M2-005 30 June 1972: The Dow Capillary Oxygenator Clinical Trials.
8) UBTL report TR-104-5-EO-005 29 June 1972: A Physical Examination of Dow Capillary Membrane Oxygenators following Cardiopulmonary Bypass.
9) UBTL Experimental schedules 6 December 1972: 5 l/min rated DCMO Evaluation.
10) IITRI Memo with latest results requested from Dr. M.P. Kaye by Dr. C. Dennis 24 January 1973.

All the reports reviewed here have this in common: they are verbose; the language used is imprecise, leading to several possible interpretations; they are repetitive especially as far as description of technical design features are concerned; materials and methods are very poorly presented or simply omitted; tables giving experimental results do not contain all the necessary parameters while relevant data which logically should have been grouped together are disseminated throughout the reports.

Although mentioned prominently in later reports, in vitro testing described in report No. 1 was limited to H_2O, and these results are not very significant as far as blood-gas transfers are concerned.

Six 1.4 M^2 units rated at 1 liter flow were tested on partial bypass in calves. Although Hb values are not given, the extracorporeal system was primed with 500 ml blood and 500 ml Ringers resulting in minimal hemodilution. The tests were inconclusive however, because of extreme variability in venous inlet O_2 saturation, which varied from 33 to 80%, and because of instability of the pH, which varied from normal to alkalotic. Three units had an O_2 transfer below 35 ml/min/M^2, one had an O_2 transfer below 40 ml/min/M^2 and only one approached the required value of 50 ml/min/M^2. Table III (page 31) shows measured S_aO_2 values greater than 100% (??) corresponding to p_aO_2 values as low as 91 mmHg. This leaves serious doubts concerning the accuracy of the measurement technique used.

Examination of the DCMO's revealed that the open area of the capillaries represented only 22% of the total cross sectional area. In addition, there was an abrupt area increase between entrance tube and cross sectional area bounded by the tube sheet, leading to flow separation, localized stagnation of blood, and clotting. Large areas devoid of fibers, non-uniform distribution of fibers, and non-uniform entry angles were also observed. Significant

deposits (10 to 40% of cross sectional area) were found on the inlet side of all six units as well as on the outlet side (from minimal to 10-40%).

In the next phase, 13 arrays of 2 parallel DCMO's (each having an exchange area 4.2M^2; rated flow 3 l/min/unit) were tested on total bypass in calves by IITRI and the results sent to UBTL for analysis -- (report No. 2). This report contains the statement that "UBTL is not aware of a hard and fast performance specification for the DCMO. The Dow Chemical documentation states however that the 1.4M^2 model should be able to oxygenate 1 liter of blood/min. from 65% to 95% saturated at normal hematocrit and should transfer 50 ml O_2/min. It also says that the oxygenator is capable to transferring more than 50 ml O_2/min. if S_vO_2 falls below 65% or the flow rate is increased above one liter/min. These statements are contradictory:

Let us assume -- S_aO_2 = 95%, S_vO_2 - 65%, A-V diff = 30%
Hb = 12 gm% O_2 capac = 12x1.34=16.1 Vol % O_2
Flow = 1 l/min (exchange area = 1.4M^2)

$$O_2 \text{ transfer} = \frac{16.1 \times 30 \times 10}{100}$$

= 48.3 ml O_2/min or 34.5 ml O_2/min/M^2
(not counting dissolved O_2 in plasma)

Therefore if the effective O_2 transfer capacity of 1.4 M^2 is 48.3 ml/min a decrease of S_vO_2 below 65% will result in a decrease of S_aO_2 below 95%. If the flow is increased above 1 l/min with S_vO_2 constant, the O_2 transfer will increase but the rapid fall of S_aO_2 below 90% will make it useless. The second statement would be true only if the evaluation were to show that 1.4 M^2 has an O_2 transfer capacity larger than 48.3 ml/min in which case the difference would constitute a reserve capability.

Of 13 arrays tested, 2 arrays failed to perform according to specification, and for unexplained reasons no analysis was performed in six of the calf experiments. In the remaining five experiments, 54 data samples were obtained of which only 18 were within the limits established for flow and blood Hb. Grading of these 18 samples resulted in 4 failures, 7 non-conclusive and 7 pass.

This report does not give tables of measured values, and the actual O_2 transfers could not be found. A quantitative evaluation of performance and reserve capability was therefore impossible. Such an evaluation was however performed in a third study (report No. 6) at Brown University (Richardson-Galletti) and at the rated blood flow (hematocrit 33-42%) of 3 liters/min the O_2 transfer was found to be 125 ml/min or 41 ml O_2/l flow or 30 ml O_2/min/M^2 exchange area. On the basis of the previous example, this confirms that when whole blood is used the DCMO has no reserve capability at the rated flow.

As in the previous series, severe inlet thrombus deposits, graded from 3 to 5, were observed.

A review of these results by a Task Force in September, 1971, concluded that these studies were inconclusive, that the animals used (91 - 110 Kg)

were too large and therefore under-oxygenated. It recommended further tests on calves weighing only 80 kilos (177 lbs.), which was a roundabout way of admitting that at the rated blood flow the O_2 transfer was inadequate. Although this point is not clear, it seems that the use of filters on both the inlet and outlet sides of the DCMO's was also recommended. In view of the magnitude of thrombus formation and the preponderance of the deposits on the inlet side, it is surprising that no investigations were initiated into the disturbing possibility that the DCMO might cause the release from the traumatized blood, or might leach out, a substance triggering blood cell aggregation within the circulatory system of the animal itself.

The results of this additional study are given in report No. 5 but in a totally inadequate fashion. This series included:

15 animals; 4 hr total bypass; 2//3 l DCMO without filters
10 animals; 4 hr total bypass; 2//3 l DCMO with filters
10 animals; 4 hr total bypass; bubble oxygenator without filters

However:

1) The type of bubble oxygenator is not specified, nor is the type of animal.
2) Four animals subjected to bypass with the bubbler died of air embolism, indicating a serious deficiency in surgical technique.
3) It is stated that the animals subjected to bypass with the DCMO's plus filters survived, but the fate of those where no filters were used is not specified, although a continuous rise in pressure gradient across the DCMOs during bypass and heavy inlet deposits were observed.
4) Experimental results are given as mean values in terms of days pre-op and days post-op. Hematological data (tables 8 and 9) obtained before and during bypass do not include HcT or Hb content of the blood.
5) In the graphs where pre-op and post-op data were plotted, it is not possible to tell which is the line corresponding to the bubbler and which is that corresponding to the DCMO plus filters. The values indicated by the graphs do not correspond to the numbers mentioned in the text.
6) Was there hemodilution or not? (priming fluids not mentioned; pre-bypass and per-bypass HcT or Hb values not given) From table 8 and 9, I extracted the following data:

DCMO	Bubbler
S_vO_2 = 67%	S_vO_2 = 62%
S_aO_2 = 99%	S_aO_2 = 99%
Flow = 4.05 liters/min	Flow = 3.45 liters/min
O_2 transfer = 207 cc/min	O_2 transfer = 220 cc/min

Discounting the dissolved O_2:

Since

$$O_2 \text{ transfer cc/min} = \frac{\text{Hb (gm\%)} \times 1.34 \times SO_2 \text{ A-V diff} \times \text{flow (liters)} \times 10}{100}$$

Therefore

$$\text{Hb} = \frac{O_2 \text{ transfer} \times 100}{1.34 \times SO_2 \text{ A-V diff.} \times \text{flow} \times 10}$$

and

Hb (DCMO) = 11.9 gm% Hb (bubbler) = 12.9 gm%

On the basis of these calculations, I conclude there was only moderate hemodilution. However, in this series, the 2 parallel DCMO's were used at only 66% of specified flow rate capability. This confirms previous indications that 2 parallel DCMO's having a total exchange area of 8.4 M^2 can oxygenate 4 L blood/min. Whether they can oxygenate 6 L/min is problematic (as flow is increased in an oxygenator, the time available for gas exchange decreases). On the basis of the Galetti report indicating a maximum of 230-250 cc O_2 transfer/min for 2 parallel DCMO's, it would appear that in this series at 4 L of blood flow (Hb = 12.5 gm%) the units were operating very close to optimal capacity.

None of these studies makes any mention of the temperature of the blood in the DCMO's. Since this parameter determines eventual shifts in the blood O_2 dissociation curve, the lack of this datum must necessarily affect evaluation of the results obtained.

Reports No. 7 and 8 deal with clinical trials at Utah and comparison of the DCMO (13 patients) and Bentley (10 patients) oxygenators during open heart surgery in 23 human patients. All patients survived short term bypass (up to 2 1/2 hours) and the results are described as extremely satisfactory.

However, description of the methodology used is incomplete. From Table III, I extracted the following data:

	DCMO	Bentley
Dextrose-Isolyte E priming vol:	3.1 liters	2.1 liters
Hb during bypass decreased to	46% of control	59.9% of control
Hemodilution	54%	40.1%
Mean S_aO_2	98.9%	97.2%
Mean p_aO_2	334 mmHg	137 mmHg
Mean S_vO_2	81.4%	79.6%
Mean P_vO_2	56.5 mmHg	39.6 mmHg
Mean SO_2 A-V diff.	17.5%	17.6%
Mean Flow	5.6 l/min	5.4 l/min
Mean Art. Blood P	75 mmHg	86 mmHg
Mean O_2 transfer	112 cc/min	101 cc/min
Mean Patient weight	170 lbs	165 lbs.

This indicates:

1) Excessive hemodilution in both groups.
2) Lower than average p_aO_2's for the Bentley.
3) Possible error in measurement technique
   in DCMO group p_vO_2 57 S_vO_2 = 81
   in Bentley group p_vO_2 40 S_vO_2 = 80*
4) The 2 parallel DCMO's were operated at rated flow capacity of 6 liters (2x3 liters) and this barely maintained blood pressure at 75 and 86 mmHg respectively. With such high flows, the A-V diff. decreases (17.5% because the S_vO_2 tends to increase (80%) and at this high level of hemodilution the S_aO_2 values tend to lose significance.
5) During bypass, the very low O_2 uptakes in relation to patient weights raise the unanswered questions whether or not hypotherima was used and whether or not higher normothermic body O_2 requirements could have been

* S_vO_2 = 80% with P_vO_2 = 40 mmHg at 37°C would require a ph_v of 7.5. This would be very doubtful in venous blood.

satisfied by the DCMO. It is to be noted that the Bentley is capable of better performance than that indicated here.

6) At these levels of hemodilution, any comparative evaluation loses much of its significance.

Conclusions

1) After 2 years of testing and evaluation, the data available do not permit a definite performance characterization of the DCMO. The data are incomplete, and testing was not done under standardized conditions according to rigid scientific criteria.
2) The performance of the T & E facilities was very unsatisfactory. The testing that was done was very expensive and the return in terms of valid comparative results is poor. A better methodology and a more appropriate sequence in the methods used would have been much more productive.
4) Although filters and hemodilution can alleviate the problem, the properties of the DCMO are very disturbing since they remain unexplored. Prospects for long-term perfusion do not seem encouraging for this reason.
5) The effects of the DCMO on the constituents of blood have not been fully or satisfactorily explored.
6) Although the DCMO has been used clinically under special conditions, its performance must be rated as marginal until the limits of its performance can be ascertained in a more scientific way.
7) The DCMO does not perform any better than currently available clinical oxygenators. Whereas it requires the presence of filters, the Bentley was used clinically without filters. It does have the advantage of being more compact.
8) Clinical trials may have been premature.

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January 30, 1973

Data reviewed March 20, 1973.